PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for an online randomized controlled trial among non-treatment seeking problem gamblers: training inhibition in online problem gambling (TRAIN-online) trial.
AUTHORS	Santiago, Antoine; Carre, Arnaud; Miranda, Ruben; Lemogne, Cédric; LeStrat, Yann; Benyamina, Amine; Perney, Pascal; Luquiens, Amandine

VERSION 1 – REVIEW

REVIEWER	rodda, simone University of Auckland, School of Population Health
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	This is a protocol for an RCT examining the impact of an internet intervention for problem gambling. The intervention delivers cognitive behavior therapy involving engagement with bi-weekly activities and telephone support. Participants will be recruited from the community and will score greater than 5 on the PGSI indicating moderate risk or problem gambling. It sounds like this will be an interesting study that offers a new approach for the treatment of problem gambling. The manuscript could be strengthened in terms of how the aims and processes of the study will be carried out. Overall the biggest issue is English language making it difficult to understand the study. I think that some of the expressions on core parts of the intervention description / process is not quite right which hampers evaluation of the protocol. It would be ideal to have the protocol heavily edited by a native English speaker with the researchers so as to ensure the intended meaning captured in the protocol. Grammarly might be a good start to get some of the content sorted. The abstract introduces terms that should be explained. It states that the intervention is cognitive training targeting inhibitory skills but there is nothing in the introduction that says what this is or why you would do it. The abstract also states that it will be compared with a neutral sensorial program but it is not clear if this is a placebo app or an active control. It seems being able to track account based gambling data is novel – but there is no explanation of this or statement that a gambling operator is involved. The second last sentence refers to non-treatment seeking gamblers which I am guessing is the current sample. This can't be right given they are treatment seeking by participating in the study.

	Highlights say that guidance is optional but this isn't stated in the abstract. It says their focus is transferability to real life but there is no information to suggest the app isn't providing skills for real life – why does it need to be transferred? Speaks to the importance of describing the intervention focus succinctly and so that it is clear in the abstract. Highlights refer to SST – no information provided on what this abbreviation is. Introduction. There are abbreviations not explained. The introduction is a bit mixed and could better explain the nature of the intervention type, the mechanisms of change or exactly how it works online. There is reference to it being helpful in real world situations but it could be clearer. I've read it three times and I'm still unsure. The second last paragraph says it would be helpful for online gamblers – why? The last paragraph says that internet based rcts are an emerging design – I don't think this is quite correct as there are a dozen trials now in gambling. These studies should be included and something said about how the current study is different. Also there is the implication multiple times that the intervention is 'fully online' but the abstract says that a person will be involved providing support. The research aims say that it will assess the efficacy of the evaluation at 0 weeks but I don't think this can be correct. Methods Study design says it is a national online research – this is not clear to an international audience. There is reference to ANJ but this is not a known term – could you say who they are and how they are involved. There is no information on consent / eligibility based on release of account information. This seems like an invasion of privacy and must have consent. In terms of recruitment – doesn't this mean only people who gamble at that site are eligible? This is not in the inclusion critters. What if the person wants to participate but does not want to share their account data or has two accounts or bets offshore? There is no information on the wording for study recruitment which would later limit this studies risk of bias assessment. That is will participants know what group they are in based on recruitment information? Randomisation is a bit unclear. If the paper is assessed for ROB it will be judged as not providing sufficient information on how randomisation sequence was generated and the involvement of the researchers in randomisation process. Screening and trial flow are a bit repetitive and appear to present contradictory information. For example it says oral consent and then 'check a box'. Now it refers to a phone debriefing – which is different to the abstract and different to the highlights section. Trial flow has different dates on gambling data than the aims. Intervention description starts out with quite a lot of unexplained jargon and brand names. It would be good to clarify what this is and also the involvement of these companies in this study. Are they providing the content for free or is this paid for? It is really unclear to me how the described content relates to gambling behaviors and why the intervention would be expected to change quality of life or indeed gambling behaviors. Perhaps I'm missing something and there are gambling messaging in the intervention content. There is no detail provided on how participants access the intervention, what exactly they do each time. It would be very difficult to replicate the study based on the detail provided.

	Measures – given the PGSI recent is the main outcome measure it would be helpful to say something on the psychometric of the screen. For example I don't see how in a month there could be major change to constructs like "have you felt like you had a problem" could change in a month. If it did change – wouldn't this be a reason for treatment drop out? The reference is for the original scale – no evidence / reference for an adaption of the PGSI. I don't quite understand why guidance would be assessed by number and length of calls. The protocol says that debriefing is optional therefore assessing it by number of calls seems a false evaluation. It would be perhaps better to assess the satisfaction with the calls and then control for the number of calls in later analysis or something like that. The paragraph on program dropout seems contradictory to the previous paragraph that says there will be a 55% attrition. It states that there was no public involvement in the research but one would expect involvement from the gaming operator in terms of what data you can get and when as well as the providers of the intervention. With a complex app like this – there really was no user testing? There is no information on how blinding for statistical analysis will be done. Discussion – this starts about talking about medication which seems odd given this is not the focus of the study. I think the discussion should start out talking about the intervention and why it is different to the other dozen that have already been done and how it builds on this literature. Most of the discussion repeats other information in the document.

REVIEWER	Donnachie, Craig University of Glasgow, School of Social and Political Sciences
REVIEW RETURNED	23-Jun-2021

GENERAL COMMENTS	Study protocol for an online randomized controlled trial among non-treatment seeking problem gamblers: training inhibition in online problem gambling (TRAIN-online) trial. Gambling behaviour is increasingly becoming a public health issue. There is an urgent need for further research to understand gambling harms and develop evidence-based interventions. This study reports on the protocol for a single blinded, randomized controlled trial of a web-based therapeutic intervention to reduce online problem gambling. While the intervention study is well described, I have identified several areas of the manuscript that require further clarification. I hope my comments and suggestions are useful to the authors as they progress their manuscript. Introduction Page 3, lines 11-13: While gambling disorder is indeed a major challenge in public health, gambling-related harms are also emerging as a broader consequence of the ubiquity of gambling in Western culture and beyond, thus warrants recognition (i.e. in addition to gambling disorder). For instance, see the following

	wider definition: 'Gambling related harms are the adverse impacts from gambling on the health and wellbeing of individuals, families, communities and society' (see - https://www.bmj.com/content/365/bmj.l1807) Page 3, lines 17-19: Please include further data relating to the French context specifically. For instance, what forms of regulation are in place and who is responsible for upholding these, especially online gambling. Further, what kind of online gambling is most salient in France (e.g. sports or casino games) and among whom (male vs female, age range etc)? For instance, there is some emerging evidence indicating that young adults are particularly vulnerable to (online) gambling harms. Also, please specify what 'ODJ' refers to (i.e. national study). Page 3, lines 39-48: Please provide greater justification as to why cognitive training may be particularly effective for gambling disorder as well as outlining what this training would involve specifically. Page 4, 33-37: 'Fully Internet-based randomized controlled trial is an emerging design that could be particularly relevant and acceptable in this population, for whom the Internet is the medium of addictive behavior' – The internet is a broad medium which includes smart phone applications, PC computers, tablets etc). Some further context around these technologies would be beneficial as well as highlighting key changes in the past few years which have led to such a proliferation of online technology and gambling behaviour (including online apps and more recently the COVID-19 pandemic/restrictions). Page 4, lines 39-42: 'We propose a web-based, randomized, controlled, single-blinding clinical trial, assessing the efficacy of cognitive training program targeting inhibition, in patients with problem gambling' – Refers to a very broad population of online gamblers (very general), thus suggest including more key inclusion criteria in this sentence (e.g. age-range, PGSI score). Aims and objectives Page 4, Lines 44-60: What types of gambling behaviour will be assessed (e.g. the amount/frequency and time spent gambling)? Page 4, line 60: When you refer to '0, 6 and 14 weeks' do you mean following baseline or after the intervention has ceased? Please specify the timeline (i.e. in reference to the first week of the intervention). Page 5, lines 8-10: In line with established frameworks would it not have more advantageous to explore if the intervention were indeed acceptable and feasible among the target population? It appears that the secondary aim (number 4) could actually have been one of the main objectives of this research (i.e. to examine the acceptability of the program/intervention among the target population). Please explain how acceptability was assessed. Methods and Analysis Page 5, Line 18: 'Our study is a national online research'. This sentence appears incomplete i.e. should it read as 'online research study'?

	Page 5, 21-23: 'The French online gambling regulation authority' – please introduce earlier in the Introduction and/or describe the role and context of this authority in more detail. Page 5, lines 28-29 – 'Willing gambling service providers regulated by the ANJ and the ANJ will propose a communication on the study on their website to promote the study' – this sentence is difficult to follow, hence suggest editing/rewording. Page 5, lines 30-31 – Did you consider also using online social media platforms to communicate/promote the study? If not, why? Page 8, line 24: Measurement instruments – are these capable of detecting change over time? Page 9, lines 50-52: 'If the test application conditions are not met, a Wilcoxon test will be applied' – Could you describe the rationale for possibly using a Wilcoxon test in more detail? For instance, please confirm if you are referring to violating assumptions of normality (i.e. non-normally distributed data). Analysis of secondary outcomes Page 9, lines 54-60: No information is given on how the feasibility and acceptability of the intervention will be assessed (i.e. secondary objective 4). For instance, some form of process evaluation or follow-up qualitative interviews could have assisted in assessing the intervention acceptability as well examining how the intervention might be optimised. Discussion Page 10, lines 47-51: While online interventions have some clear merit and benefits, there have been several limitations identified that are inherently faced when devising online interventions (e.g. engagement). I suggest including some further recognition of these issues as well as consideration of how these may be addressed within the current online intervention. Page 10, lines 51-55: How will the intervention content be adapted to explore the impact of the COVID-19 pandemic given this is likely going to have considerable magnitude in influencing online gambling behaviour, particularly among vulnerable groups (there is emerging evidence to support this, hence I suggest incorporating some recent literature e.g. https://pubmed.ncbi.nlm.nih.gov/33859126/).

VERSION 1 – AUTHOR RESPONSE

REVIERWER 1

We would like to thank you for taking the time to assess our manuscript. We addressed all the concerns you raised.

Comment 1: Overall the biggest issue is English language making it difficult to understand the study. I think that some of the expressions on core parts of the intervention description / process is not quite right which hampers evaluation of the protocol. It would be ideal to have the protocol heavily edited by

a native English speaker with the researchers so as to ensure the intended meaning captured in the protocol. Grammarly might be a good start to get some of the content sorted.

Response: Thank you for your recommendation. We revised different parts of the manuscript to better explain our study. As recommended, a native English-speaking medical writer has edited the manuscript.

Comment 2: The abstract introduces terms that should be explained. It states that the intervention is cognitive training targeting inhibitory skills but there is nothing in the introduction that says what this is or why you would do it. The abstract also states that it will be compared with a neutral sensorial program but it is not clear if this is a placebo app or an active control. It seems being able to track account based gambling data is novel – but there is no explanation of this or statement that a gambling operator is involved. The second last sentence refers to non-treatment seeking gamblers which I am guessing is the current sample. This can't be right given they are treatment seeking by participating in the study.

Response: Thank you for your comment. We have revised the abstract accordingly (**Pg 2, Ln 19-42**). Concerning the participants, they are considered non-treatment seeking insofar as they are recruited after being informed of the existence of the study by gambling operators, newspapers, radio programs or gamblers online forums, and not through healthcare settings.

Comment 3: Highlights say that guidance is optional but this isn't stated in the abstract. It says their focus is transferability to real life but there is no information to suggest the app isn't providing skills for real life – why does it need to be transferred? Speaks to the importance of describing the intervention focus succinctly and so that it is clear in the abstract. Highlights refer to SST – no information provided on what this abbreviation is.

Response: Thank you for your comment. We have revised the highlights accordingly. We also added more information in the introduction to better explain the notion of transferability. Transferability refers to the fact that training inhibitory control (with tasks that do not include gambling-related stimuli) will improve both gambling behavior and general self-regulation difficulties (e.g., emotion dysregulation or impulsivity).

Change: **[Pg 3, Ln 61-67]** An optional guidance by phone performed by a trained neuropsychologist is proposed and focuses on the transferability of the inhibitory control tasks in the patient's ~~real life~~ real-life situations related to self-regulation difficulties.

Completion of an online neuropsychological assessment (~~with the SST~~ using a Stop Signal Task ~~task~~) with ~~no~~ out face-to-face contact is a challenge and limits the interpretation of the participant's cognitive abilities.

Comment 4: Introduction. There are abbreviations not explained. The introduction is a bit mixed and could better explain the nature of the intervention type, the mechanisms of change or exactly how it works online. There is reference to it being helpful in real world situations but it could be clearer. I've read it three times and I'm still unsure. The second last paragraph says it would be helpful for online gamblers – why? The last paragraph says that internet based rcts are an emerging design – I don't think this is quite correct as there are a dozen trials now in gambling. These studies should be included and something said about how the current study is different. Also there is the implication multiple times

that the intervention is ‘fully online’ but the abstract says that a person will be involved providing support. The research aims say that it will assess the efficacy of the evaluation at 0 weeks but I don’t think this can be correct.

Response: Thank you for your comment. We revised different parts of the introduction to better explain the nature of the intervention and the mechanisms of change.

Changes: [Pg 3, Ln 70-87] Gambling disorder and gambling-related harms, defined as the adverse impacts from gambling on the health and wellbeing of individuals, families, communities and society[1], represent~~s~~ a major challenge in public health, ~~with a human and social considerable burden~~. Despite guidelines for responsible gambling standards[2], ~~online problem and pathological gambling is an increasing challenge to healthcare providers because of its significantly increasing prevalence.[3-5] T~~the prevalence of gambling disorder is on the rise and was estimated in 2014 at 1.9% of the general French population aged 15 to 75.[3] The most popular gambling games in France are lottery games, far ahead of horse or sports betting, casino and poker. Online gambling affects two million French people, the majority of whom are young men (75.8%), and 45.4% of online gamblers are under 35 years old versus 31% of offline gamblers. The development of online gambling could be linked to the increasing role of the internet and new technologies, particularly during the Covid-19 crisis. Indeed, a recent review showed an increase in online gambling during the pandemic for three groups: younger gamblers, male gamblers and gamblers with higher severity of problem gambling.[4] More generally, ~~Online~~ online gambling may be more likely to contribute to problem gambling than offline environments.[5]

Despite these alarrming data, the treatment gap is concerning~~,~~: according to the ~~ODJ~~ Observatoire Des Jeux (French monitoring center for gambling) national survey[6], only 2% of French problem gamblers seek medical care.

[Pg 4-5, Ln 123-134] The most explored ~~lead~~ interventions are ~~is~~ cognitive bias modification and cue-specific motor response inhibition[25], which are considered specific tasks using addiction-related stimuli. ~~However, practicing a non-specific task of self-control (i.e. avoiding sweets and tightening a handgrip) could prevent relapse in smokers.~~ Noel et al. (2013) showed a significant effect of ~~an~~ non-specific inhibition tasks on decision-making in patients with alcohol use disorder and problem gamblers.[26] ~~Interestingly, the tasks assessed were not specifically designed for a substance or a behavior. That means that~~ Thus, training on ~~a~~ tasks ~~that does not refer~~ unrelated to any substance or ~~to any~~ addictive behavior ~~could improve addiction symptoms. It would imply~~ should lead to both improvement of the addiction itself and better transferability of the enhanced skills to ~~daily life and~~ other behaviors and contexts as they are not limited by addiction-related stimuli but target ~~as a~~ general and transdiagnostic psychological processes.[27] ~~in the psychopathological outcomes~~.

Comment 5: Methods Study design says it is a national online research – this is not clear to an international audience. There is reference to ANJ but this is not a known term – could you say who they are and how they are involved. There is no information on consent / eligibility based on release of account information. This seems like an invasion of privacy and must have consent. In terms of recruitment – doesn’t this mean only people who gamble at that site are eligible? This is not in the inclusion critters. What if the person wants to participate but does not want to share their account data or has two accounts or bets offshore? There is no information on the wording for study recruitment which would later limit this studies risk of bias assessment. That is will participants know what group they are in based on recruitment information? Randomisation is a bit unclear. If the paper is assessed for ROB it will be judged as not providing sufficient information on how randomisation sequence was generated and the involvement of the researchers in randomisation process.

Response: Thank you for your comment. We revised different parts of the Methods section to provide more precise information.

Changes: [**Pg 6, Ln 177-186]** Our study is a ~~national online research. It is a~~ therapeutic web-based, comparative, randomized controlled trial, 2 arms, single ~~blinding~~ blinded, with 52 weeks of follow-up~~:~~. Data will be collected from ~~(1)~~ clinical assessments at baseline, and weeks 6 and 14~~; (2)~~, and gambling account based data extracted from the French online gambling regulation authority (ANJ) at baseline, week 6, 14 and 52. The ANJ is the regulatory authority supervising online gambling in France. It approves and controls all online gambling games and stores the player account data of all online gaming operators. With participant consent, only player account data from legal online gaming operators (approved by the ANJ) will be extracted. Participants who do not have a player account from an approved gaming operator will be included in the study, but no player account data will be extracted for them.

[Pg 7, Ln 204-210] A single-blind ~~Randomization~~ randomization will be made by a medical doctor investigator via a central web-based system called Cleanweb®. Cleanweb® is a secure web-based system used for randomization and research data storing. Research data, including adverse events, is thus stored in an electronic Case report Form (e-CRF). Treatment (cognitive training or control intervention) will be allocated according to a computer-generated randomization list with a 1:1 ratio, ~~balanced by~~ using blocks of random size. Only the investigators know which participants are in the cognitive training or control intervention group.

[Pg 7, Ln 212-231] There is no screening visit. Any gambler willing to participate in the study will have to contact the medical doctor investigator by email~~. The~~, who will send back the information notice. In the same email, the investigator will ~~ask for emailing back~~ request their telephone number in order to perform the inclusion visit by phone.

~~Patients who have consent and fulfilling all inclusion and exclusion criteria will be included by phone. A medical doctor will call back the gambler to explain the study, and the gambler will be able to ask any question on the study purpose, design, scheduling, intervention, following steps, data collection processes. The person's free and informed oral consent will be obtained by phone the person is enrolled on the study. Inclusion criteria will be checked. The person will specifically confirm his consent by ticking the box indicating that he freely accepts to participate on the online e-clinical register form (e-CRF) (Cleanweb®).~~

Consent will be obtained in a two-step process: an oral consent by phone and an online confirmation in the web-based system Cleanweb®. After being given all the relevant study information (study purpose, design, scheduling, intervention, following steps, data collection processes) the person's free and informed oral consent will be obtained by the medical doctor during the inclusion visit by phone. Then, if the inclusion and exclusion criteria are fulfilled, the person will be called back within three days by a neuropsychologist investigator to complete the initial assessment (baseline) in Cleanweb®. Prior to completing the questionnaires in Cleanweb®, the participant will confirm their consent by ticking a box indicating that they freely accept to participate.

Comment 6: Screening and trial flow are a bit repetitive and appear to present contradictory information. For example it says oral consent and then 'check a box'. Now it refers to a phone debriefing – which is different to the abstract and different to the highlights section. Trial flow has different dates on gambling data than the aims.

Response: Thank you for your comment. We revised this section accordingly.

Comment 7: Intervention description starts out with quite a lot of unexplained jargon and brand names. It would be good to clarify what this is and also the involvement of these companies in this study. Are they providing the content for free or is this paid for? It is really unclear to me how the described content relates to gambling behaviors and why the intervention would be expected to change quality of life or indeed gambling behaviors. Perhaps I'm missing something and there are gambling messaging in the intervention content. There is no detail provided on how participants access the intervention, what exactly they do each time. It would be very difficult to replicate the study based on the detail provided.

Response: Thank you for your comment. We added more information to clarify the intervention description. In particular, we clarify that the tasks do not have gambling-related stimuli. They are meant to train a general cognitive ability (inhibitory control) and not the gambling behavior itself.

Changes: [**Pg 8-9, Ln 261-283]** The cognitive training is a computerized cognitive training targeting inhibitory control of motor response, ~~which has been elaborated~~ developed in collaboration with a software provider ~~of softwares~~ for neuropsychological applications (Scientific Brain Training®). It ~~has been~~ is derived ~~by the~~ from one of their existing validated programs called "PRESCO"[30] ~~Presco® HappyNeuron~~. ~~by SBT~~. ~~Two screen captures from the cognitive program can be seen in **figure 2**~~. Scientific Brain Training® and Paris University Hospital (AP-HP) are co-owners of this program. There is then no fee to access it. The tasks included in ~~the~~ this program have been selected and modified to target inhibition and ~~be~~ are adapted to the population of gamblers whose executive impairments are ~~less important~~ lower than those encountered in substance use~~d~~ disorders.[31] More challenging tasks avoid ceiling effect and could thus enhance patients motivation to progress over the training. The tasks are contextualized and gamified. ~~Patients must train twice a week for an advised duration of 30-minutes, for six weeks. The tasks are contextualized and gamificated.~~ They are non-specific tasks, which do not have gambling-related stimuli. Indeed, the experimental intervention focuses on the training of the general inhibitory control ability, which is supposed to play a role not only in gambling behaviors but also in other self-regulation difficulties related to daily life. Two screen captures from the cognitive program can be seen in **figure 2**.

A link will be sent by email to the participant to install the software on their computer. The participant will access the cognitive program with a login identifier created by the neuropsychologist. Participants will be able to access the program at any time, but must train twice a week for an advised duration of 30 minutes, for six weeks. During training sessions, the participant will be able to choose one or more tasks to perform. Debriefing calls will be proposed by the neuropsychologist, according to the participant's wishes. Up to two 15-minute scheduled appointments a week will be planned.

Comment 8: Measures – given the PGSI recent is the main outcome measure it would be helpful to say something on the psychometric of the screen. For example I don't see how in a month there could be major change to constructs like "have you felt like you had a problem" could change in a month. If it did change – wouldn't this be a reason for treatment drop out? The reference is for the original scale – no evidence / reference for an adaption of the PGSI.

Response: Thank you for your comment. We have added more information to clarify the use of the PGSI recent for our study.

Change: [**Pg 10-11, Ln 334-340]** The primary ~~judgement criterion~~ outcome measure is the change over 6 weeks in the PGSI-recent, a French translation and modified version of the Problem Gambling Severity Index (PGSI)[32] with a 30-day~~s~~ recall period, self-completed ~~on the e-CRF~~ online in Cleanweb®. PGSI has been identified as a tool to measure change in problem gambling.[33] The

original scale has a 12-month recall period. This period was shortened to 30 days for our study. The PGSI consists of nine items which are assessed on a four-point scale: never (1), sometimes (2), most of the time (3) almost always (4). The total score ranges from 0 to 27.

Comment 9: I don't quite understand why guidance would be assessed by number and length of calls. The protocol says that debriefing is optional therefore assessing it by number of calls seems a false evaluation. It would be perhaps better to assess the satisfaction with the calls and then control for the number of calls in later analysis or something like that.

Response: Thank you for your comment. We decided to make the debriefing optional because our previous findings suggest possible adverse effects of imposed guidance among problem gamblers in an online clinical trial (Luquiens et al. 2016). In this context, we assume that number and length of calls represent intensity criteria and are considered as a change factor. We agree that assessing guidance by number and length of calls has limitations (e.g., we cannot know why some participants refuse the debriefings) and will be careful with our analyses and conclusions.

Change: [P11 L364-366] Level of guidance will be assessed by the number and ~~the~~ length of debriefing calls. We assume that number and length of calls represent intensity criteria and are considered as a change factor.

[Pg 12-13, Ln 396-409] ~~The number and the length of training sessions (acceptability) and the number and length of debriefing sessions (level of guidance) will be described in each arm, and compared using t-tests or Wilcoxon tests, as appropriate.~~ According to Sekhon et al. (2017), 'if an intervention is considered acceptable, patients are more likely to adhere to treatment recommendations and to benefit from improved clinical outcomes'.[39] Thus, we consider the number and the length of training sessions and dropout rate as proxies for acceptability. Indeed, we assume that if the patient perceived the program as effective, he would implant the intervention in his daily life. According to Simons and Kursawe (2019), feasibility is 'the proportion of patients who were offered treatment who completed and the number of sessions attended'.[40] Thus, we will use the number of training sessions and the number of debriefing calls as a measure of feasibility. The number and the length of training sessions, the dropout rate and the number of debriefing calls will be described in each arm, and compared using t-tests or Wilcoxon tests~~, as appropriate~~ if data are non-normally distributed.

Comment 10: The paragraph on program dropout seems contradictory to the previous paragraph that says there will be a 55% attrition.

Response: Thank you for pointing this out. We revised the paragraph as follows.

Change: **[Pg 12, Ln 373-375]** Anticipated 55% maximum for loss to follow-up at 6 weeks. Except for those who withdraw their informed consent, ~~there will be no program dropouts and~~ all participants allocated to either study condition will be included in intention-to-treat (ITT) analyses.

Comment 11: It states that there was no public involvement in the research but one would expect involvement from the gaming operator in terms of what data you can get and when as well as the providers of the intervention. With a complex app like this – there really was no user testing?

Response: Thank you for your comment. We revised this section accordingly.

Change: [**Pg 13, Ln 412-417]** Patients ~~and public~~ were not involved in designing and conducting this research. The French online gambling regulation authority (ANJ) and the willing gaming operators regulated by it are involved in the recruitment process by sharing a communication about the study on their websites. They also share player account data collected during the study (up to 52 weeks after inclusion). Scientific Brain Training® provides the experimental and control programs (which have been adapted for the study) and the software associated.

Comment 12: There is no information on how blinding for statistical analysis will be done.

Response: Data entered into the database (Cleanweb) are locked and cannot be changed by the investigators. Statistical analyses will not be blinded.

Comment 13: Discussion – this starts about talking about medication which seems odd given this is not the focus of the study. I think the discussion should start out talking about the intervention and why it is different to the other dozen that have already been done and how it builds on this literature. Most of the discussion repeats other information in the document.

Response: Thank you for you comment. We revised different parts of the discussion to better focus on our intervention and explain how it is different from other online interventions **[Pg 13-14-15, Ln 437-490]**.

We would like to **thank you again** for taking the time to review our manuscript.

REVIEWER 2

We would like to thank you for taking the time to assess our manuscript. We addressed all the concerns you raised.

Comment 1: Introduction Page 3, lines 11-13: While gambling disorder is indeed a major challenge in public health, gambling-related harms are also emerging as a broader consequence of the ubiquity of gambling in Western culture and beyond, thus warrants recognition (i.e. in addition to gambling disorder). For instance, see the following wider definition: 'Gambling related harms are the adverse impacts from gambling on the health and wellbeing of individuals, families, communities and society' (see - https://emea01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.bmj.com%2Fcontent%2F365%2Fbmj.l1807&data=04%7C01%7C%7C4a3964aa035c4e5cd24108d9623d85a2%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C637648838644306405%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=LCXU0JiouIS9pjSNISIFpYq5QNs8vOnUXvl0Z0u23vU%3D&reserved=0)

Response: Thank you for your recommendation. We added the notion of gambling-related harms at the beginning of our introduction.

Change: **[Pg 3, Ln 70-75]:** Gambling disorder and gambling-related harms, defined as the adverse impacts from gambling on the health and wellbeing of individuals, families, communities and society[1], represent~~s~~ a major challenge in public health, ~~with a human and social considerable burden~~. Despite guidelines for responsible gambling standards[2], ~~online problem and pathological gambling is an increasing challenge to healthcare providers because of its significantly increasing prevalence.[3-5]~~

Comment 2: Page 3, lines 17-19: Please include further data relating to the French context specifically. For instance, what forms of regulation are in place and who is responsible for upholding these, especially online gambling. Further, what kind of online gambling is most salient in France (e.g. sports or casino games) and among whom (male vs female, age range etc)? For instance, there is some emerging evidence indicating that young adults are particularly vulnerable to (online) gambling harms. Also, please specify what 'ODJ' refers to (i.e. national study).

Response: Thank you for your comment. We added more data relating to the French context and specify what ODJ means.

Change: **[Pg 3, Ln 75-84]** ~~T~~the prevalence of gambling disorder is on the rise and was estimated in 2014 at 1.9% of the general French population aged 15 to 75.[3] The most popular gambling games in France are lottery games, far ahead of horse or sports betting, casino and poker. Online gambling affects two million French people, the majority of whom are young men (75.8%), and 45.4% of online gamblers are under 35 years old versus 31% of offline gamblers. The development of online gambling could be linked to the increasing role of the internet and new technologies, particularly during the Covid-19 crisis. Indeed, a recent review showed an increase in online gambling during the pandemic for three groups: younger gamblers, male gamblers and gamblers with higher severity of problem gambling.[4] More generally, ~~Online~~ online gambling may be more likely to contribute to problem gambling than offline environments.[5]

Comment 3: Page 3, lines 39-48: Please provide greater justification as to why cognitive training may be particularly effective for gambling disorder as well as outlining what this training would involve specifically.

Response: Thank you for your comment. We revised the introduction to better justify our intervention.

Change: **[Pg 4-5, Ln 119-141]** ~~Despite the robust data documenting the inhibition deficit in addictive disorder, very few data are available on the efficacy of cognitive training tasks or programs targeting inhibition skills. However,~~ ~~Nora~~ Volkow ~~and her team~~ and Morales (2015) ~~supported~~ demonstrated the therapeutic potential in addiction, including gambling disorder, of cognitive training ~~interventions~~ that targets and improves self-regulation skills.[24] The most explored ~~lead~~ interventions are ~~is~~ cognitive bias modification and cue-specific motor response inhibition[25], which are considered specific tasks using addiction-related stimuli. ~~However, practicing a non-specific task of self-control (i.e. avoiding sweets and tightening a handgrip) could prevent relapse in smokers.~~ Noel et al. (2013) showed a significant effect of ~~an~~ non-specific inhibition tasks on decision-making in patients with alcohol use disorder and problem gamblers.[26] ~~Interestingly, the tasks assessed were not specifically designed for a substance or a behavior. That means that~~ Thus, training on ~~a~~ tasks ~~that does not refer~~ unrelated to any substance or ~~to any~~ addictive behavior ~~could improve addiction symptoms. It would imply~~ should lead to both improvement of the addiction itself and better transferability of the enhanced skills to ~~daily life and~~ other behaviors and contexts as they are not limited by addiction-related stimuli but target ~~as a~~ general and transdiagnostic psychological processes.[27] ~~in the psychopathological outcomes~~. ~~From a transdiagnostic point of view inhibitory control is a core vulnerable process of substance and behavioral addictions which could be thus trained with durable effects in both treatment and prevention of addiction as well as in daily life activities.~~ In a recent study, Penolazzi et al. (2020) tested the transdiagnostic hypothesis of inhibitory control deficits in gambling disorders.[28] The results show preserved memory inhibition and impaired motor response inhibition, a pattern of deficits opposite to that previously

reported for substance used disorders. These findings suggest that cognitive training targeting motor and visuospatial inhibitory control could be more adapted to online gamblers.

Comment 4: Page 4, 33-37: 'Fully Internet-based randomized controlled trial is an emerging design that could be particularly relevant and acceptable in this population, for whom the Internet is the medium of addictive behavior' – The internet is a broad medium which includes smart phone applications, PC computers, tablets etc). Some further context around these technologies would be beneficial as well as highlighting key changes in the past few years which have led to such a proliferation of online technology and gambling behaviour (including online apps and more recently the COVID-19 pandemic/restrictions).

Response: Thank you for your comment. We revised this section accordingly.

Change: [Pg 3, Ln 79-83] The development of online gambling could be linked to the increasing role of the internet and new technologies, particularly during the Covid-19 crisis. Indeed, a recent review showed an increase in online gambling during the pandemic for three groups: younger gamblers, male gamblers and gamblers with higher severity of problem gambling.[4]

Comment 5: Page 4, lines 39-42: 'We propose a web-based, randomized, controlled, single-blinding clinical trial, assessing the efficacy of cognitive training program targeting inhibition, in patients with problem gambling' – Refers to a very broad population of online gamblers (very general), thus suggest including more key inclusion criteria in this sentence (e.g. age-range, PGSI score).

Response: Thank you for your comment. We revised this sentence accordingly.

Change: **[Pg 5, Ln 146-149]** We propose a web-based, randomized, controlled, single-~~blinding~~ blinded clinical trial, assessing the efficacy of a cognitive training program targeting inhibition, in ~~patients with problem gambling aged~~ gamblers older than 18 years old and with a Problem Gambling Severity Index-recent (PGSI) ≥5.

Comment 6: Aims and objectives Page 4, Lines 44-60: What types of gambling behaviour will be assessed (e.g. the amount/frequency and time spent gambling)?

Response: Thank you for your comment. We revised this section accordingly.

Change: **[Pg 5-6, Ln 158-165]** To assess the efficacy on the evolution of the gambling behavior assessed by the account player-based gambling data, at 6, 14 and 52 weeks from baseline. Gambling behavior includes: total deposit, compulsivity (defined three consecutive deposits within 12 hours), number of deposit in the hour following the stake, total loss per game, number of sessions (a session is defined as a gambling behavior where the beginning of a session starts when a gambling action occurs after no gambling action for at least 30 minutes, and the end of the session is a gambling action followed by no gambling action for 30 minutes), session duration and gambling time slot.

Comment 7: Page 4, line 60: When you refer to '0, 6 and 14 weeks' do you mean following baseline or after the intervention has ceased? Please specify the timeline (i.e. in reference to the first week of the intervention).

Response: Thank you for your comment. We revised this section accordingly. We added "from baseline" after "14 weeks" **[Pg 5, Ln 167-169]**.

Comment 8: Page 5, lines 8-10: In line with established frameworks would it not have more advantageous to explore if the intervention were indeed acceptable and feasible among the target population? It appears that the secondary aim (number 4) could actually have been one of the main objectives of this research (i.e. to examine the acceptability of the program/intervention among the target population). Please explain how acceptability was assessed.

Response: We agree with the reviewer that acceptability of the intervention is an important factor, but as we were particularly interested in the efficacy of this technique, we chose this outcome measure for our primary study objective. The acceptability of this program and the preferred level of guidance of the non-treatment seeking problem gamblers is evaluated according to the number and length of training sessions.

Comment 9: Methods and Analysis Page 5, Line 18: 'Our study is a national online research'. This sentence appears incomplete i.e. should it read as 'online research study'?

Response: Thank you for your comment. We revised this sentence accordingly.

Change: **[Pg 6, Ln 177-178]** Our study is a ~~national online research. It is a~~ therapeutic web-based, comparative, randomized controlled trial, 2 arms, single ~~blinding~~ blinded, with 52 weeks of follow-up~~:~~.

Comment 10: Page 5, 21-23: 'The French online gambling regulation authority' – please introduce earlier in the Introduction and/or describe the role and context of this authority in more detail.

Response: Thank you for your comment. We added more information about the ANJ.

Change: **[P6 L181-186]** The ANJ is the regulatory authority supervising online gambling in France. It approves and controls all online gambling games and stores the player account data of all online gaming operators. With participant consent, only player account data from legal online gaming operators (approved by the ANJ) will be extracted. Participants who do not have a player account from an approved gaming operator will be included in the study, but no player account data will be extracted for them.

Comment 11: Page 5, lines 28-29 – 'Willing gambling service providers regulated by the ANJ and the ANJ will propose a communication on the study on their website to promote the study' – this sentence is difficult to follow, hence suggest editing/rewording.

Response: Thank you for your comment. We edited this sentence for a better understanding.

Change: **[P6 L189-182]** ~~Willing gambling service providers regulated by the ANJ and the ANJ will propose a communication on the study on their website to promote the study.~~ Both willing gambling operators regulated by the ANJ as well as the ANJ itself, will publish a communication on their websites to promote the study.

Comment 12: Page 5, lines 30-31 – Did you consider also using online social media platforms to communicate/promote the study? If not, why?

Response: Thank you for your comment. We added the social media platforms used to promote the study.

Change: **[P6 L186-188]** The communication will also be promoted in newspapers, radio programs, ~~and gamblers~~ gambling online forums and online social media platforms (Facebook, LinkedIn, Instagram).

Comment 13: Page 8, line 24: Measurement instruments – are these capable of detecting change over time?

Response: Thank you for your comment. We added more information about our measure instruments.

Change: [P10-11 L334-340] The primary ~~judgement criterion~~ outcome measure is the change over 6 weeks in the PGSI-recent, a French translation and modified version of the Problem Gambling Severity Index (PGSI)[32] with a 30-day~~s~~ recall period, self-completed ~~on the e-CRF~~ online in Cleanweb®. PGSI has been identified as a tool to measure change in problem gambling.[33] The original scale has a 12-month recall period. This period was shortened to 30 days for our study. The PGSI consists of nine items which are assessed on a four-point scale: never (1), sometimes (2), most of the time (3) almost always (4). The total score ranges from 0 to 27.

Comment 14: Page 9, lines 50-52: 'If the test application conditions are not met, a Wilcoxon test will be applied' – Could you describe the rationale for possibly using a Wilcoxon test in more detail? For instance, please confirm if you are referring to violating assumptions of normality (i.e. non-normally distributed data).

Response: Thank you for your comment. We revised this section accordingly.

Change: **[Pg 12, Ln 388-390]** The change in PGSI-recent total score over 6 weeks will be compared with the student's t-test. ~~If the test application conditions are not met, a Wilcoxon test will be applied~~ A Wilcoxon test will be applied if data are non-normally distributed.

Comment 15: Analysis of secondary outcomes Page 9, lines 54-60: No information is given on how the feasibility and acceptability of the intervention will be assessed (i.e. secondary objective 4). For instance, some form of process evaluation or follow-up qualitative interviews could have assisted in assessing the intervention acceptability as well examining how the intervention might be optimised.

Response: Thank you for your comment. We revised this section to clarify how the feasibility and acceptability of the intervention will be assessed.

Change: **[Pg 12-13, Ln 396-409]** ~~The number and the length of training sessions (acceptability) and the number and length of debriefing sessions (level of guidance) will be described in each arm, and compared using t-tests or Wilcoxon tests, as appropriate.~~ According to Sekhon et al. (2017), 'if an intervention is considered acceptable, patients are more likely to adhere to treatment recommendations and to benefit from improved clinical outcomes'.[39] Thus, we consider the number and the length of training sessions and dropout rate as proxies for acceptability. Indeed, we assume that if the patient perceived the program as effective, he would implant the intervention in his daily life. According to Simons and Kursawe (2019), feasibility is 'the proportion of patients who were offered treatment who completed and the number of sessions attended'.[40] Thus, we will use the number of training sessions and the number of debriefing calls as a measure of feasibility. The number and the length of training sessions, the dropout rate and the number of debriefing calls will be described in each arm, and compared using t-tests or Wilcoxon tests~~, as appropriate~~ if data are non-normally distributed.

Comment 16: Discussion Page 10, lines 47-51: While online interventions have some clear merit and benefits, there have been several limitations identified that are inherently faced when devising online interventions (e.g. engagement). I suggest including some further recognition of these issues as well as consideration of how these may be addressed within the current online intervention.

Response: Thank you for you comment. We added more information about the limitations of the study and the way to address them.

Change: **[Pg 14-15, Ln 463-487]** Despite these benefits, some risks and limitations must be considered for our online study. ~~A particular~~ Particular ~~caution~~ care will be ~~ported~~ taken ~~to~~ during the ~~"launch of study"~~ first calls, when included participants will be initiated to their attributed program application, ~~but also~~ to the data collection platform, and motivated to complete all assessments including neuropsychological ones.~~, in order to avoid missing data.~~ To prevent high dropout rates and non-compliance issues, ~~Reminders~~ automatic reminders will help gamblers to complete follow-up assessments, and phone calls will be ~~performed in addition~~ made to motivate participants in assessment completion if necessary. Guidance will be available according to the participant's wishes, learning from our previous findings suggesting possible adverse effects of imposed guidance among problem gamblers participating in an online clinical trial.[11] ~~And avoid high attrition rates~~.

~~We chose to document efficacy from different perspectives: clinical ones, i.e. subjective patient-reported outcomes and very objective account-based gambling data, and neuropsychological assessments~~. Moreover, ~~Completion~~ completion of neuropsychological assessments with ~~no~~ out face-to-face contact is a challenge. A cautious analysis of the whole group will be performed to document parameters of the task in this special setting. We will recommend completing the assessments from ~~a very one~~ the same computer, with similar conditions of internet access at the three time points. Another limitation is that we cannot know why some participants refuse the debriefings. We will therefore be cautious about the conclusions drawn from the statistical analyses of guidance.

~~Guidance has been left to the participant's convenience, learning from our previous findings suggesting possible aversive effect of imposed guidance among problem gamblers participating to a clinical trial with no face to face.~~

We will also take into consideration the influence of Covid-19 pandemic on gambling behavior[4] with secondary analyses of the socio-demographic and gambling characteristics of gamblers included during the lockdowns in France.

Comment 17: Page 10, lines 51-55: How will the intervention content be adapted to explore the impact of the COVID-19 pandemic given this is likely going to have considerable magnitude in influencing online gambling behaviour, particularly among vulnerable groups (there is emerging evidence to support this, hence I suggest incorporating some recent literature

e.g. https://emea01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F33859126%2F&data=04%7C01%7C%7C4a3964aa035c4e5cd24108d9623d85a2%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C637648838644306405%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=xYNGnYZrsJrEydHnzY%2BEK0%2BWcE7rbvM7n11vy1Gfc4E%3D&reserved=0).

Response: Thank you for your comment. Unlike offline clinical trials, movement restrictions related to the COVID-19 pandemic have little impact on the content of our study since it is conducted online. However, as you rightly point out, the COVID-19 pandemic does have an influence on online gambling behavior. Therefore, we plan to conduct secondary analyses of the data of gamblers included during the lockdowns in France. We will compare the socio-demographic and gambling characteristics of gamblers included during the lockdowns with those included outside these periods. **[Pg 15, Ln 485-487]**

We would like to **thank you again** for taking the time to review our manuscript.

VERSION 2 – REVIEW

REVIEWER	rodda, simone University of Auckland, School of Population Health
REVIEW RETURNED	11-Oct-2021

GENERAL COMMENTS	Thank you for responding to my comments on the previous version of this paper. I am satisfied that my comments have been addressed. There are just two minor wording changes that have been made that you might like to reconsider. Page 1, line 28 perhaps correct 'online gambling affects…' to something indicating that 2 million people from France gamble online (it doesn't necessarily "affect" them per se). Paragraph 2 of the introduction – perhaps rethink 'alarming' as it think this is overstating involvement in online gambling (which is a legal activity).

REVIEWER	Donnachie, Craig University of Glasgow, School of Social and Political Sciences
REVIEW RETURNED	25-Oct-2021

GENERAL COMMENTS	I am satisfied the authors have thoroughly addressed my concerns and suggestions. I have no other comments other than to thank the authors for the opportunity to read their interesting work.